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A REVIEW ON ASYMMETRIC ORGANOCATALYSIS

HISTORICAL WORKS AND PRESENT SCENARIO

[1]Pranshu Vishwakarma*, [2]Abhishek Verma

[1]Student, Department of Chemistry, K.B.P.G. College, Mirzapur (U.P.), 231001

[2]Assistant Professor, Department of Chemistry, K.B.P.G. College, Mirzapur (U.P.), 231001

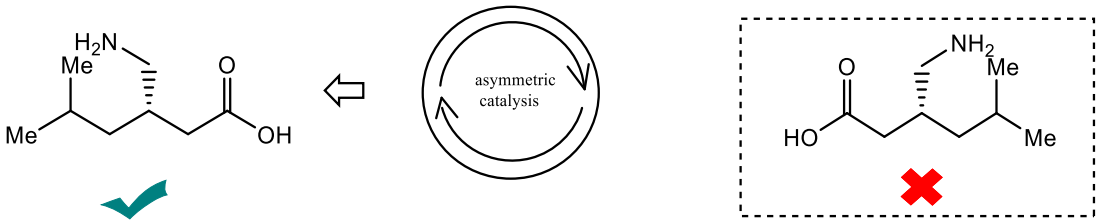
Abstract: After introducing the background of "Asymmetric Organocatalysis," this review delves into significant historical events and breakthroughs spanning from 1912 to 2021. It then shifts focus to the Nobel Prize-winning contributions of David MacMillan and Benjamin List, specifically their advancements in Amine-Catalyzed Asymmetric Diels-Alder Reaction (Iminium ion Activation) and Proline-Catalyzed Direct Asymmetric Aldol Reaction (Enamine Activation). These advancements hold significant importance in medicinal and pharmaceutical fields, offering a promising pathway for the enantioselective synthesis of new drugs. Moreover, by integrating organocatalysis with photoredox catalysis, electrocatalysis, and machine learning (A.I.), novel activation modes and catalytic methods are anticipated to emerge in the near future.

Keywords: Asymmetric organocatalysis, enantioselective, catalyzed reactions.

Introduction

Structures exhibiting non-superimposability with their mirror images, thereby existing as two enantiomers, are termed chiral (previously referred to as *asymmetric* in older literature). A chiral environment is a prerequisite for asymmetric synthesis[1]. Catalysis stands as a foundational concept in chemistry, whereby the rate of a chemical reaction is enhanced by the inclusion of a catalyst that remains unconsumed throughout the process. Asymmetric catalysis represents a method for synthesizing enantiomerically pure compounds catalytically[2]. In this process, a chiral catalyst selectively accelerates the formation of one mirror-image isomer[3].

Asymmetric catalysis is “the science of making molecules as one mirror image”.



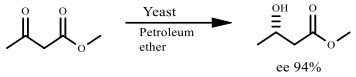
There are three pillars of asymmetric catalysis:-

Asymmetric catalysis

- Bio-catalysis
- Metal-catalysis
- Organocatalysis

Bio-catalysis

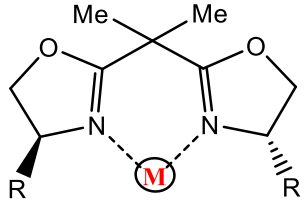
Enzyme based catalysis



In Biocatalyzed Asymmetric Catalysis, the substrate's chirality is imparted by the chiral nature of the enzyme, which serves as the catalyst. For instance, 'Yeast' functions as a biocatalyst in the enantioselective reduction of ketones[4].

Metal-catalysis

Organometallic catalysis
Asymmetric Metal Catalysis involves using chiral metal complexes to facilitate enantioselective reactions. It employs the use of metal ligand complexes derived from chiral ligands. It consists of an organic part and a metallic part.



Metal **M** = Cobalt (Co)
Ruthenium (Ru)
Copper (Cu)
Titanium (Ti)

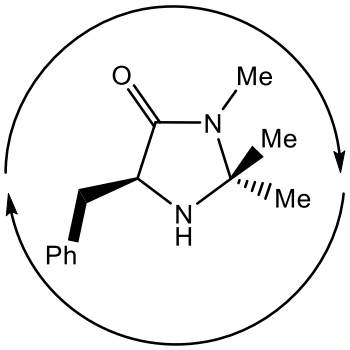
Metals have the ability to serve as coordination sites for substrates. When combined with chiral and enantiomerically pure ligands, they facilitate reactions in an asymmetric environment, thereby catalyzing them [5].
The groundbreaking advancement in asymmetric catalysis employing chiral transition metal complexes is chiefly attributed to **three scientists**, each recognized with a **Nobel Prize in 2001** for their significant contributions to this domain.

- Williams S. Knowles → Used **Rh** based catalyst
- Ryoji Noyori → Used **Ru** based catalyst
- K. Barry Sharpless → Used **Ti** based catalyst

- Asymmetric Epoxidation
- Asymmetric Dihydroxylation
- Asymmetric Aminohydroxylation

Organocatalysis

Simple small organic molecule based catalysis
Asymmetric Organocatalysis is a new and growing branch of asymmetric catalysis which employs simple chiral and enantiomerically pure organic molecules to give enantiomerically enriched product.



Imidazolidinone Catalyst

This organocatalyst when used gives high preference to the formation of one mirror image form over the other.
In metal catalysis some metals can be :-

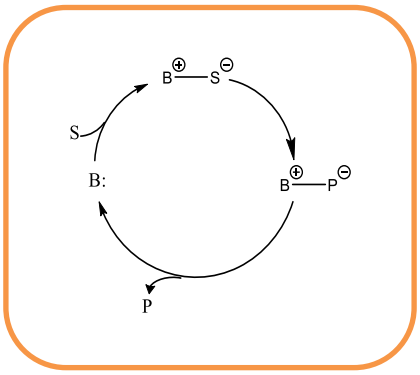
- Expensive
- Toxic
- Difficult to work with

Therefore, comes the concept of organocatalysis :-

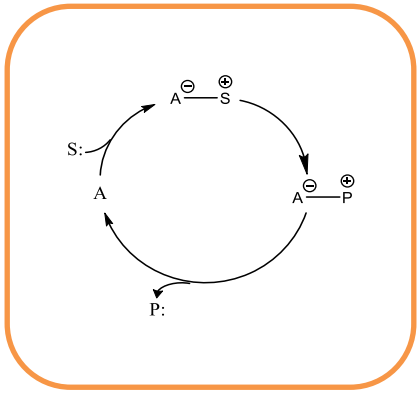
- It is readily available (from the nature's building blocks).
- It is not sensitive to air or water.
- It is inexpensive.
- It is easy to handle.
- It is non-toxic in nature (i.e. it can be readily removed from waste streams)[6].

Classification of Organocatalysis

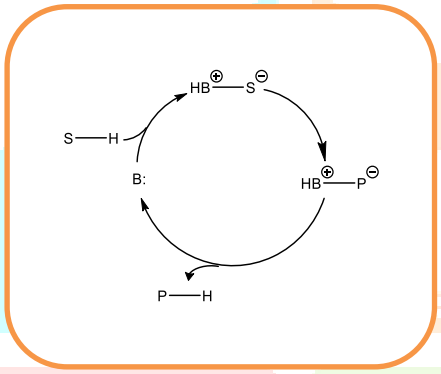
- On the basis of acid/base properties[7] :-



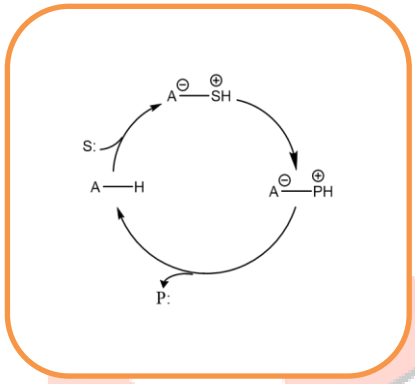
1. **Lewis Base Catalysis**



2. **Lewis Acid Catalysis**



3. **Bronsted Base Catalysis**



4. **Bronsted Acid Catalysis**

- On the basis of their mode of interaction with starting materials and reagents[8] :-

Covalent Activation
- Enamine Catalysis
- Iminium Catalysis
- Nucleophilic Catalysis
- SOMO Catalysis
- Oxidation Catalysis

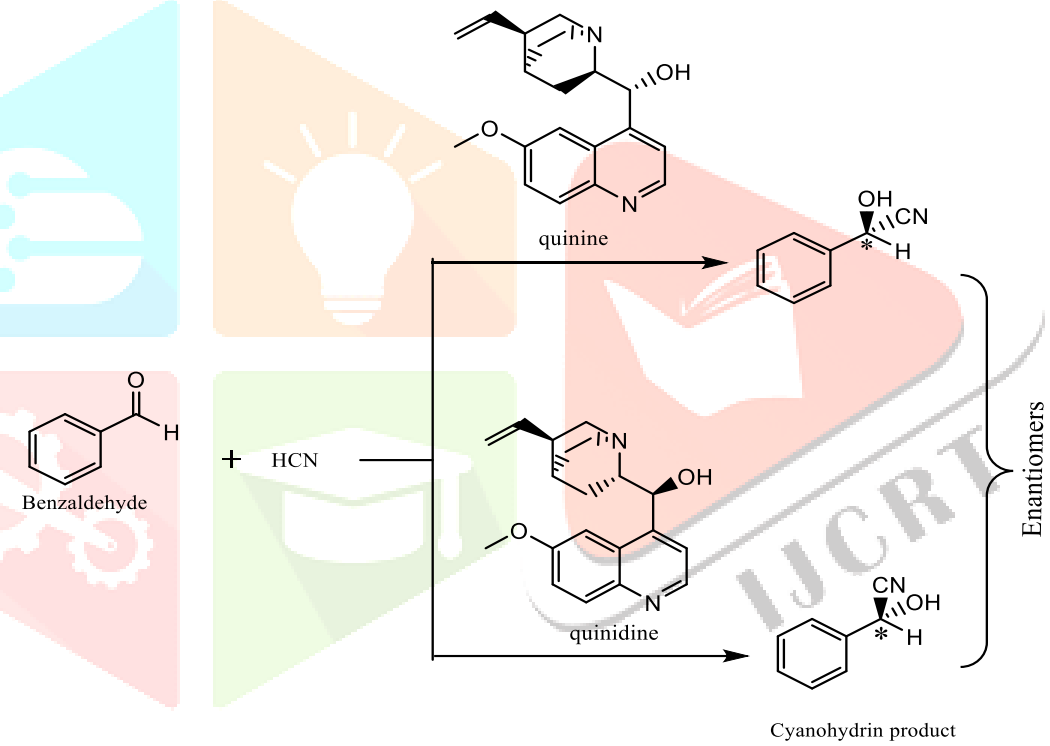
Non-Covalent Activation
- Bronsted Acids
- Bronsted Bases
- H-Bonding Catalysis
- Ion pairing (PTC)
- Halogen-bonding Catalysis

History and Development of Asymmetric Organocatalysis

1912

Bredig and **Fiske** are credited with the initial instance of employing small chiral organic molecules as catalysts. They utilized naturally occurring Cinchona alkaloids, specifically the chiral bases quinine and quinidine, to catalyze the addition of HCN to benzaldehyde, yielding the respective cyanohydrins.

The cyanohydrins produced using the chiral base catalyst 'quinine' are enantiomeric to those obtained with the chiral base catalyst 'quinidine'. However, the cyanohydrins were obtained with low enantiomeric ratios (er). This discovery was conceptually groundbreaking in this field. Despite being diastereomers, quinine and quinidine yield enantiomeric products, a characteristics that has been used with much success in asymmetric catalysis[9].

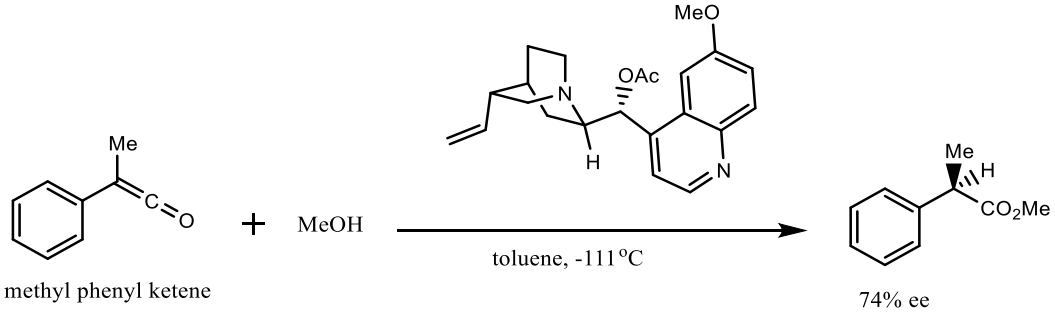


1950

Prelog reinvestigated Bredig's reaction in more detail.

1960

Pracejus reported one of the first highly enantioselective reactions ever. The method involved employing a Cinchona alkaloid (O-acetylquinine) for the reaction of methyl phenyl ketene with methanol, resulting in the formation of the corresponding methyl ester with an enantiomeric ratio of 87:13[10].



1966

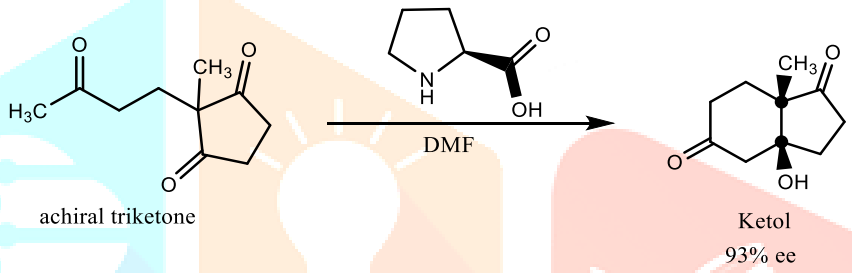
Sheehan employs chiral carbenes as catalysts to conduct a benzoin condensation reaction, yielding a product with moderate enantioselectivity[8].

1970

Until 1970, a considerable amount of information had been gathered on the catalytic functions of organic molecules but the time was not yet ripe to develop a comprehensive understanding of the area.

1971-74

Eder, **Sauer** and **Wiechert** at Schering and **Hajos** and **Parrish** at Hoffmann-La Roche independently reported the Proline-catalyzed intramolecular aldol cyclization *en route* to advanced steroid precursors. Remarkably, although Hajos and Parrish described this reaction as a "simplified model of a biological system in which (s)-Proline plays the role of an enzyme", this methodology was not developed further for almost 30 years. In Hajos-Parrish reaction, the starting material is an achiral triketone and it requires just 3% of proline to obtain the reaction product, a ketol in 93% ee[11] .
This is the first example of an amino acid-catalyzed asymmetric aldol reaction.



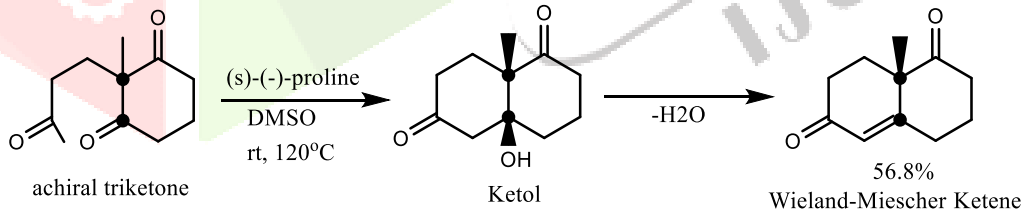
achiral triketone — Ketol, 93% ee

1975

Wynber began utilizing Cinchona alkaloids as chiral base catalysts, alongside employing their quaternary ammonium salts as chiral phase transfer catalysts.

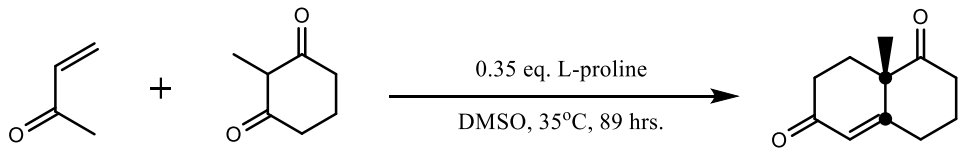
1985

A proline based asymmetric synthesis of the **Wieland-Miescher** ketone. It is actually a Hajos-Parrish reaction followed by dehydration[12].



achiral triketone — Ketol — 56.8% Wieland-Miescher Ketene

This reaction has also been performed in a one-pot procedure, leading to 49% yield and 76% ee.



49% yield
76% ee

1990

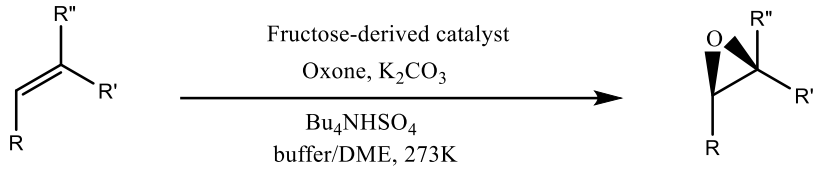
During the 1990s, there was a notable surge in the introduction of diverse asymmetric strategies catalyzed by chiral organic molecules. These included:

- **Miller's** innovative use of small peptides as catalysts for the enantioselective kinetic resolution of alcohols.

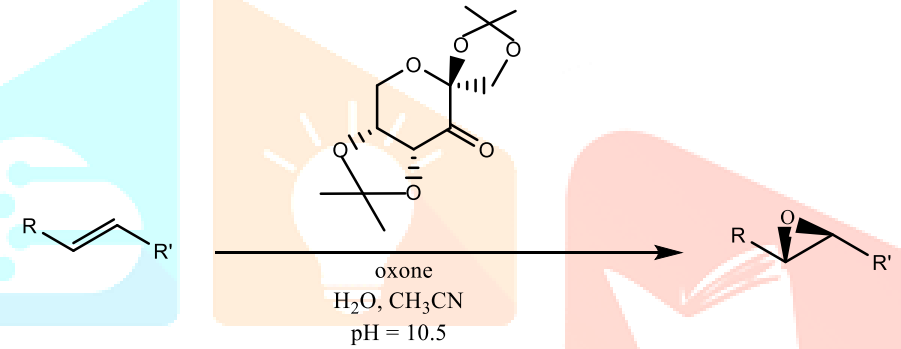
- The introduction of chiral DMAP derivatives by **Fu**, **Shi's** and **Yang's** chiral ketone-based oxidation catalysts.
- **Denmark's** chiral Phosphoramides.
- The initial reports of **Maruoka's** quaternary ammonium salt catalysis.

1997

A significant advancement in organocatalysis occurred when Yian Shi reported the first general, highly enantioselective organocatalytic reaction with the catalytic asymmetric epoxidation of *trans* and trisubstituted olefins with chiral dioxiranes[13].



Shi epoxidation with modern reaction conditions[14] :-



1998

Jacobsen and co-workers demonstrated that thiourea serves as a highly effective catalyst in the Strecker reaction involving N-allyl benzaldimine and HCN, resulting in the formation of the corresponding adduct with high yields and enantiomeric ratio[9].
This reaction is quoted as Jacobsen's seminal chiral thiourea-catalyzed Strecker reaction.
Thioureas and ureas both serve as outstanding catalysts for numerous asymmetric transformations and have been refined as bifunctional catalysts. These catalysts are capable of simultaneously activating both a nucleophile and an electrophile.

1984-2000

Introduction and establishment of different concepts (PTCs, H-Bonding, Lewis bases,……)
Collectively, these initial reports notably demonstrated the immense potential of chiral organic molecules to function as valuable catalysts in asymmetric transformations. However, as previously mentioned, these methods and catalysts were perceived more as isolated advancements within their respective domains, rather than as potential cornerstones for more universally applicable catalytic concepts that could be deployed across a wider range of applications[8].

2000-21

Now comes **Benjamin List** and **David MacMillan** bringing a new era in asymmetric catalysis in year 2000 by their work on Proline-catalyzed asymmetric intermolecular aldol reaction (Enamine-catalysis) and chiral imidazolidinone-catalyzed asymmetric Diels-Alder reaction (Iminium ion-catalysis) respectively.
These two reports and the therein presented activation concepts fundamentally changed the way how our community thinks about catalysis and synthesis.
For their work on the development of asymmetric organocatalysis, bringing it on such a level, Benjamin List and David MacMillan was awarded with Nobel Prize in Chemistry 2021.

Present Scenario : The Nobel Prize in Chemistry 2021

David MacMillan and Benjamin List were honored with the Nobel Prize in Chemistry 2021 for their groundbreaking contributions to asymmetric organocatalysis. Their pioneering work involved the creation of the first amine-catalyzed asymmetric Diels-Alder reactions and Proline-catalyzed direct asymmetric Aldol reaction, achieving remarkable levels of enantioselectivity. The organocatalysts they designed have broad applicability across a diverse array of reactions.

David William Cross MacMillan

Professor of Chemistry at Princeton University,

16 March 1968 (age 56)

Bellshill, Scotland, United Kingdom

Benjamin List

11 January 1968 (age 56)
Frankfurt, West Germany

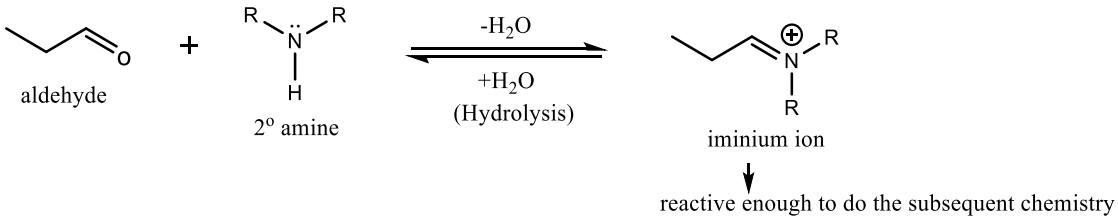
Introduction to the first highly enantioselective organocatalytic Diels-Alder reaction by David W.C. MacMillan

Since, the metal based catalysts for asymmetric inductions are expensive, toxic, sensitive to air and moisture and also need gloveboxes, inert gases, ultra-dry solvents or even high levels of experimental expertise. So, it is not a convenient way for any researcher to perform with. Anyone doing research on asymmetric metal catalysis had to spend a lot of time standing with gloveboxes for safety. So, by considering all these problems, David MacMillan thought of excluding the metal from metal catalyst strategies and wanted to bring a new way of catalysis which would be safe, economic and easily accessible for bringing asymmetric inductions. Since, a metal catalyst contains both a metal part and an organic part, so, he wanted to design the organic part alone in such a way that it would be helpful in producing enantioselective product as the organic part is inexpensive, non-toxic and does not require gloveboxes because for any large-scale catalytic process, the most salient considerations are cost and safety[15].

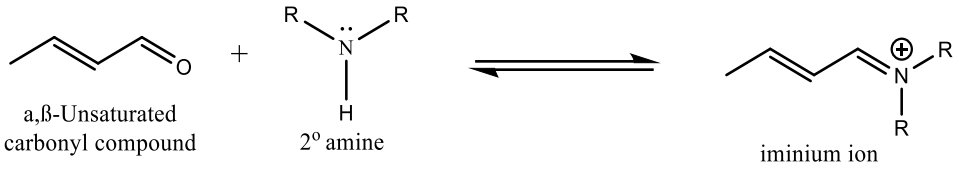
The Dawn of the Nobel Idea !!

Once, a student asked Sir David MacMillan to explain the reductive amination reaction and in response he brought a chalk and ran to the board to explain the process and that was the time which gave him the Nobel Prize winning idea and solution to the problems of handling metal-based catalysts with gloveboxes by replacing them with organic ones.

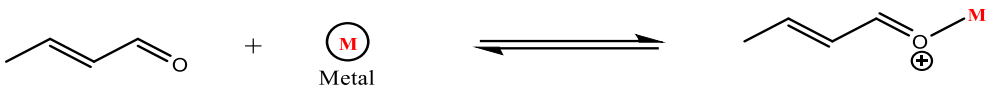
Reductive Amination Reaction – formation of iminium ion



Reversible formation of iminium ion from α,β-unsaturated aldehyde and secondary amine:-

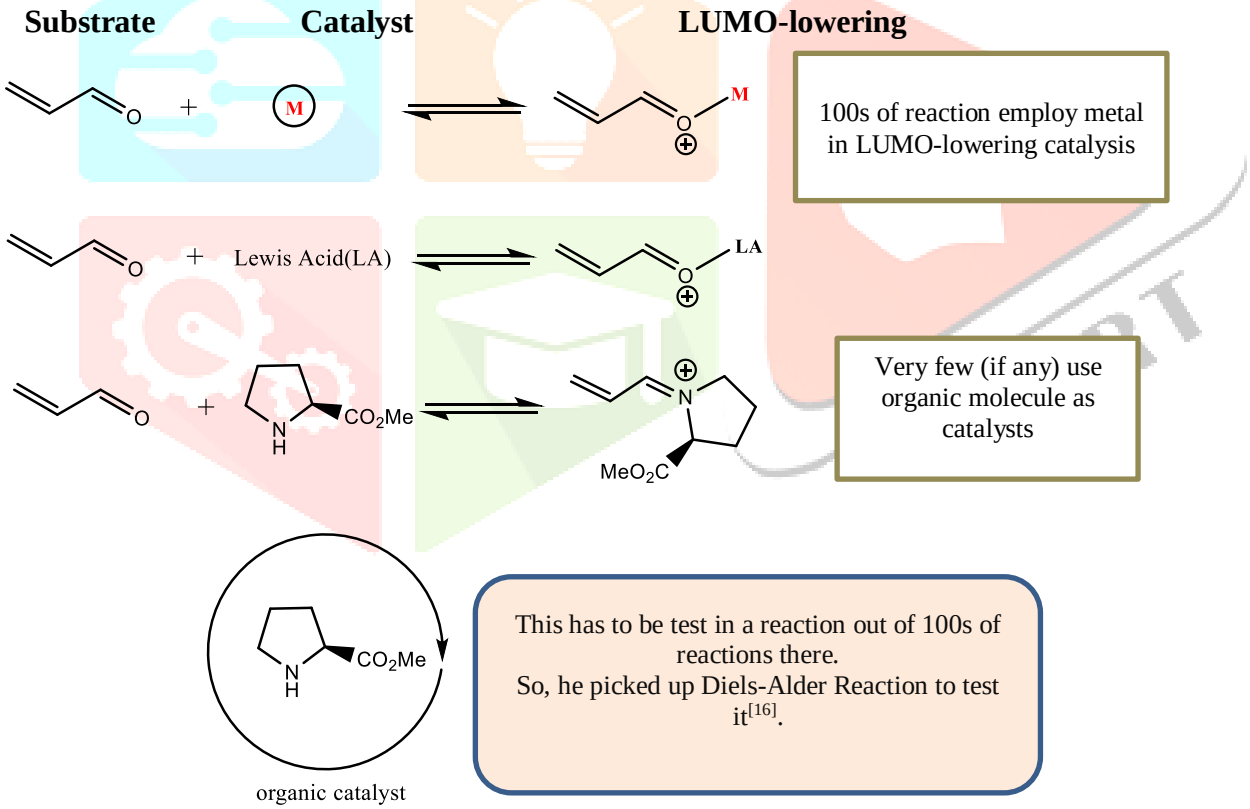


This is similar to what we do in Metal based catalysis, i.e.,

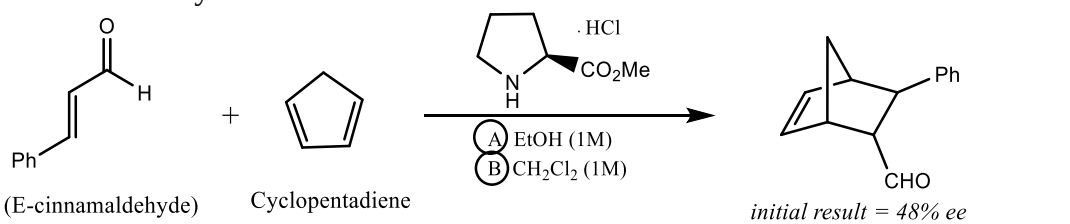


While explaining the concept, he found that the LUMO-lowering activation in iminium ion is similar to that in Metal-based catalysis. So, he got the click that if we use chiral amine instead of normal achiral amine in the above process, then the iminium ion formed will also be chiral and we can employ this chiral iminium ion as organic catalyst. Now, for checking whether the activated chiral iminium ion catalyst is useful in bringing enantioselectivity or not, he chose a very versatile reaction i.e., Diels-Alder Reaction.

LUMO Activation Concept



An amine-catalyzed Diels Alder Reaction:



initial result = 48% ee

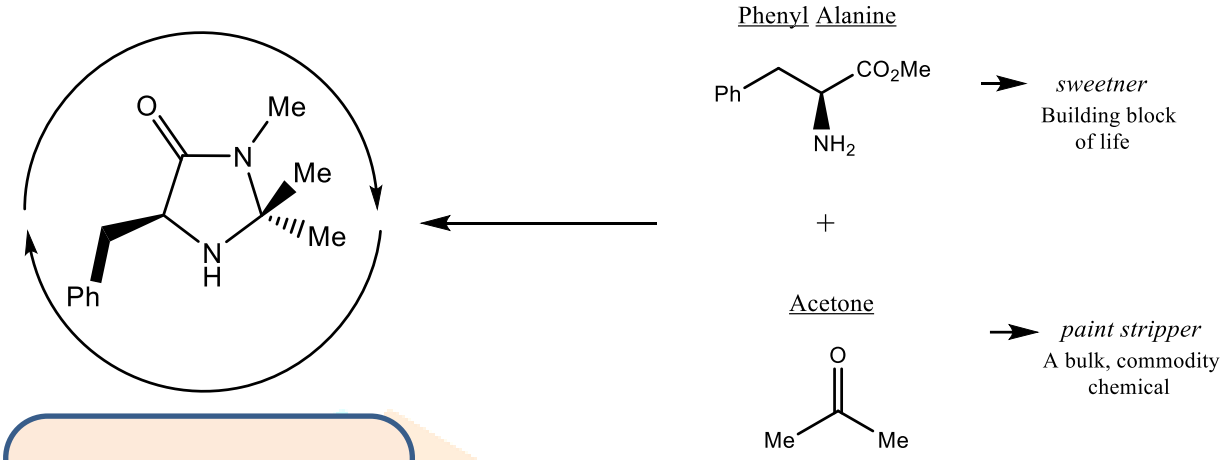
Result → Not Racemic

i.e., formation of one mirror image in preference of other

This analysis reveals that chiral amines might function as enantioselective catalysts for a range of transformations that traditionally utilize metal salts.

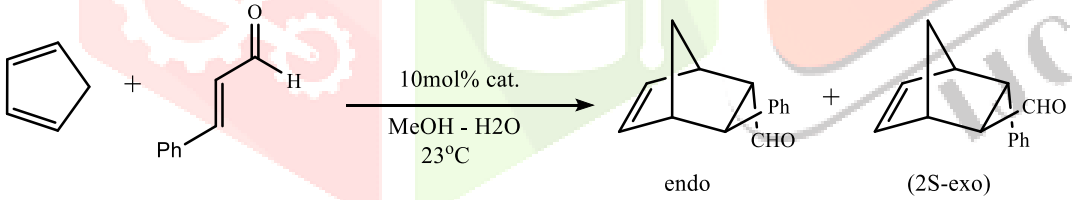
Further, he modified the chiral amine catalyst and made Imidazolidinone Catalyst which is inexpensive and can be made from easily accessible compounds- acetone and phenylalanine.

Imidazolidinone catalyst



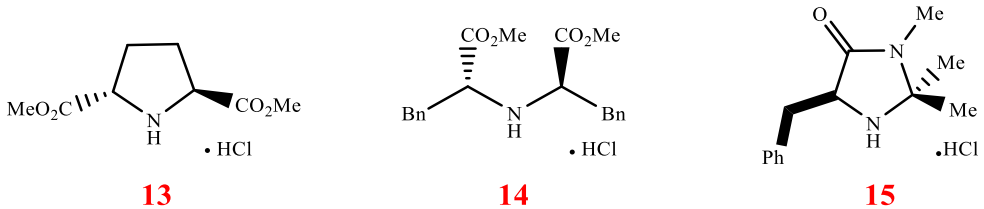
This organocatalyst when used gives high preference to the formation of one mirror image form over the other.

Our enantioselective catalytic Diels-Alder Strategy was first evaluated using cyclopentadiene with (E)-cinnamaldehyde and a series of chiral secondary amine.HCl salts[17].



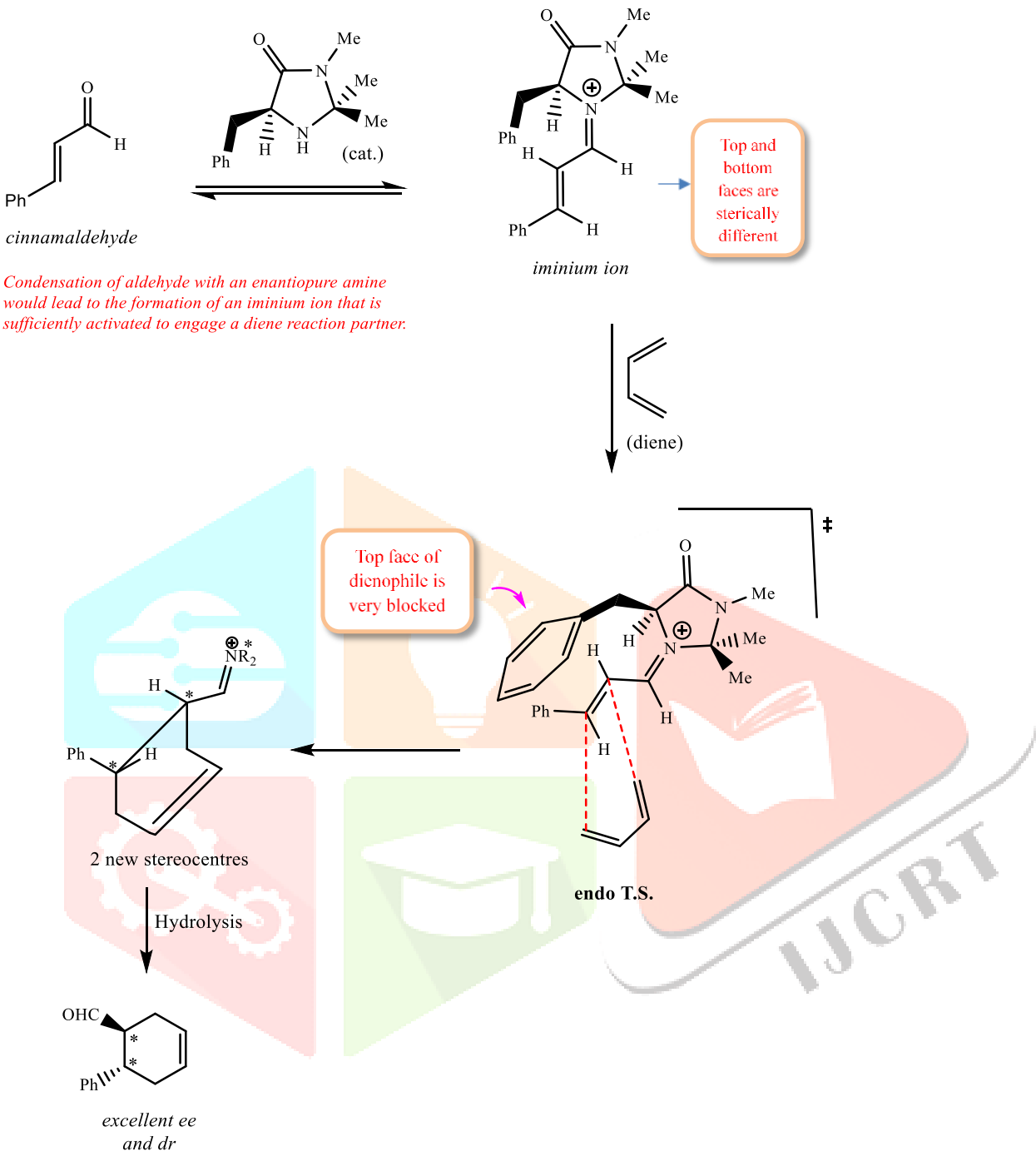
entry	catalyst	time(h)	yield(%)	exo : endo	exo ee(%)
1	(s)-Pro-OMe.HCl	27	81	2.7 : 1	48(2R)
2	(s)-Abr-OMe.HCl	10	80	2.3 : 1	59(2S)
3	**13**	23	92	2.6 : 1	57(2R)
4	**14**	84	82	3.6 : 1	74(2R)
5	**15** (5mol%)	8	99	1.3 : 1	93(2S)

Catalyst



13 **14** **15**

Mechanism of iminium catalyzed asymmetric Diels-Alder Reaction

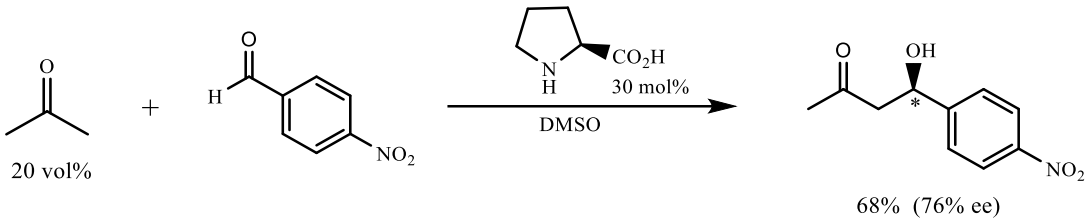


Importantly, control of iminium ion geometry through the use of steric constraints on the catalyst architecture was found to provide the highest levels of enantioselectivity while maintaining reaction efficiency.

Introduction to Proline-Catalyzed Direct Asymmetric Aldol Reactions by Benjamin List

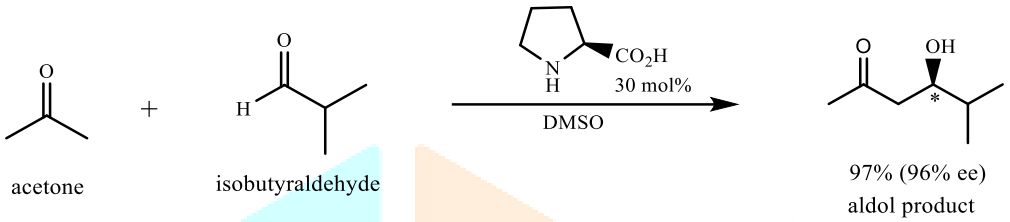
Proline, an amino acid, serves as a potent asymmetric catalyst facilitating the direct aldol reaction between unmodified acetone and a variety of aldehydes.

Benjamin List initially investigated the reaction of acetone with 4-nitrobenzaldehyde. Reacting proline (30mol%) in DMSO/acetone (4:1) with 4-nitrobenzaldehyde at room temperature for 4h furnished aldol product in 68% yield and 76% ee[18] .

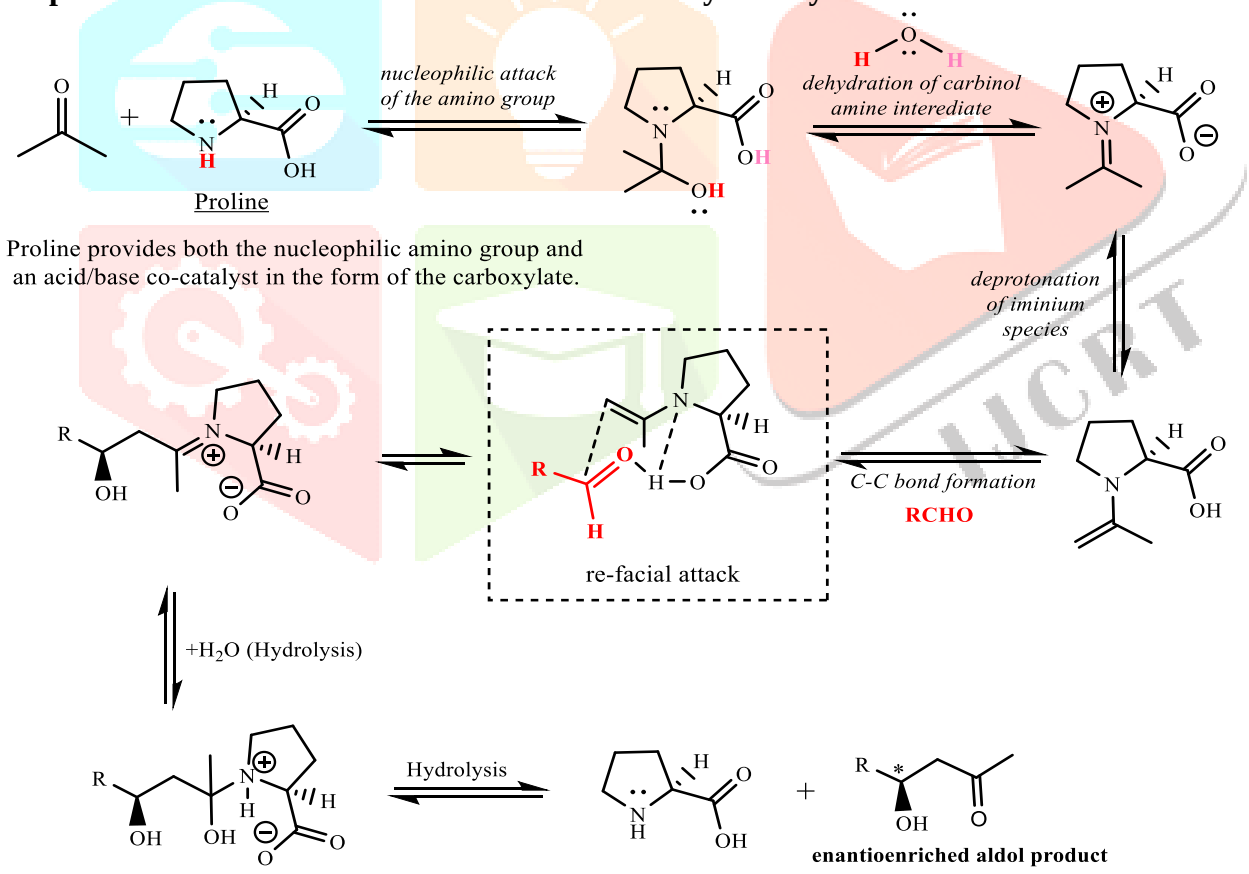


This finding is quite remarkable since it is known that proline can undergo numerous reactions with aldehydes. When Benjamin List *et al.* uses high concentration of acetone in the reaction mixture, the side reactions of proline with aldehydes were suppressed. After screening several solvents, they determined that anhydrous DMSO at room temperature provided the most favorable conditions in terms of reaction duration and enantioselectivity.

Unbranched aldehydes, such as pentanal, did not yield noteworthy amounts of the desired cross-aldol product. However, the reaction of acetone with isobutyraldehyde gave aldol product in 97% yield and 96% ee[18].



Proposed Enamine Mechanism of the Proline-Catalyzed Asymmetric Aldol Reaction

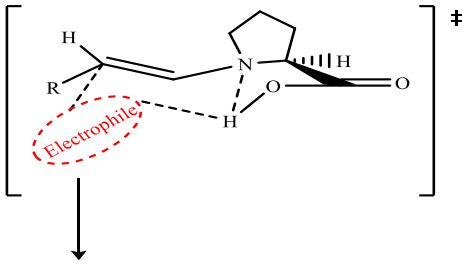


Important features of this reaction are:-

- Proline is non-toxic, cost-effective, and readily accessible in both enantiomeric forms.
- The reactions can be conducted at room temperature without the need for inert conditions.
- The catalyst is water-soluble, allowing for easy removal through aqueous extraction.
- There's potential for scaling up the reactions for industrial purposes.
- This is the initial example of a non-metallic small-molecule catalyst for direct intermolecular asymmetric aldol reactions.

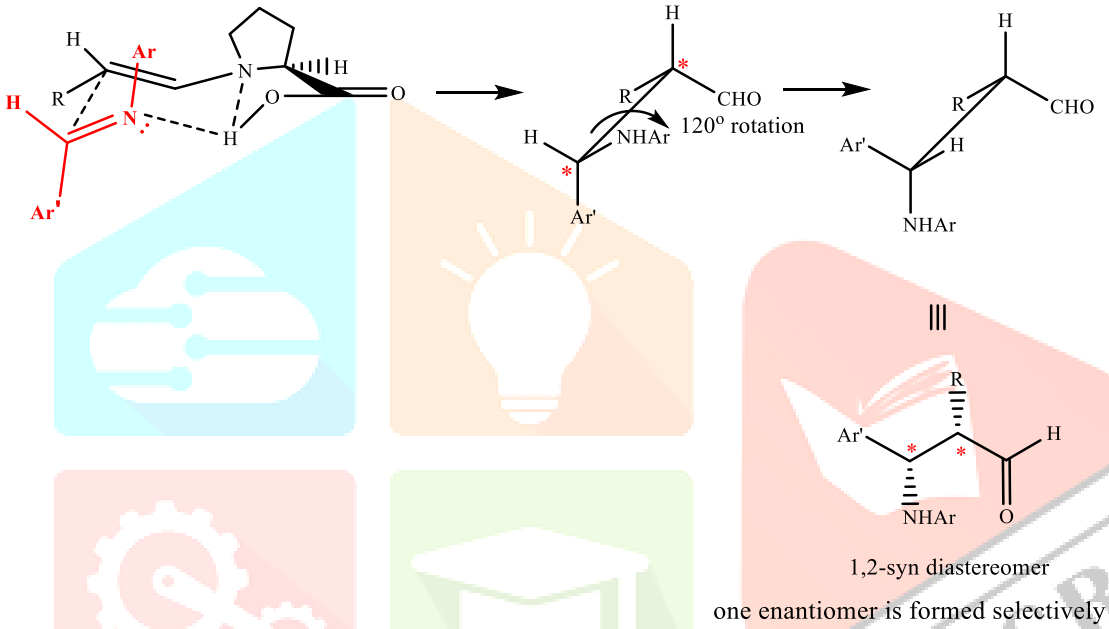
More than just aldol reactions…..

If we take aldehyde in place of acetone(ketone) in the above reaction then the 'Transition State' will look like -



Here, aldehyde was used as an electrophile in aldol reaction.
But another electrophiles can also be put here which needs to be activated.

Example-  as Electrophile.



one enantiomer is formed selectively

Futuristic scope of Asymmetric Organocatalysis

Regarding future prospects, asymmetric organocatalysts hold promise for exploring new avenues in catalysis. The innovative spirit within this domain remains vibrant, offering ingenious solutions to pertinent chemical challenges. With creativity as a constant catalyst for advancement, the synergistic integration with emerging technologies in electrochemistry, photocatalysis, and chemoinformatics is anticipated to serve as a formidable impetus for the advancement of organocatalysis in the foreseeable future[19].

Upbringing of New Activation Modes

The broad spectrum of potential interactions leading to unique substrate activation in organocatalysis continuously sparks novel ideas and designs for specific catalytic transformations[19].

Electrocatalytic Transformations

Another area with significant potential for rapid expansion in the near future is redox organocatalysis, leveraging iodine, phosphorus, or sulfur derivatives. These compounds possess the capability to mimic transition metal catalysis under certain conditions[19].

Photo-organocatalysis

The fusion of photoredox catalysis with organocatalysis, a synergy between photoredox activation and organocatalysis, presents an efficient strategy in organic synthesis. This innovative approach stands as a

formidable solution for overcoming complex chemical challenges, as demonstrated by the direct alkylation of aldehydes[19].

Chemoinformatics and machine-learning techniques in organocatalysis

Driven by enhanced computing capabilities, increased data accessibility, and advanced machine learning algorithms, artificial intelligence-based methodologies are beginning to emerge as valuable tools in chemistry. These approaches are poised to transcend prior constraints in catalyst design[19].

Advancements in organocatalysis tools will play a crucial role in fostering more efficient methods, including those that are protecting-group-free. These developments are expected to facilitate biorthogonal applications in intricate reaction environments[8].

Also, asymmetric organocatalysis have a wide range application in medicinal chemistry and pharmaceutical industries for new drug designs as a single enantiomer in an asymmetric catalytic fashion.

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